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Current stage-specific chemotherapeutic options in colon cancer

Michael J Martin

Colorectal cancer is one of the most common cancers worldwide. Until recently, chemotherapeutic treatment options were limited to various 5-fluorouracil–leucovorin combinations. However, the last 10 years have seen rapid developments in the treatment of colon cancer. These include the introduction of two additional chemotherapeutic agents, irinotecan and oxaliplatin. Additional agents have been developed, namely the targeted therapies in the form of the monoclonal antibodies bevacizumab and cetuximab. The oral forms of chemotherapy (i.e., capecitabine and uracil-tegafur) have been demonstrated to be as efficacious as traditional intravenously administered 5-fluorouracil. As a result, the number of possible treatment options available to patients has increased dramatically. The aim of this review is to report the currently accepted stage-specific chemotherapeutic treatment options for colon cancer, the evidence for these regimens and future developments.

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Medical Oncology Clinical Research Unit and Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 6120 Executive Blvd EPS, Rm 7016, Rockville, MD 20852, USA
Tel.: +1 301 451 9732
Fax: +1 301 496 1854
martmich@mail.nih.gov

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Colorectal cancer is one of the most common cancers diagnosed in economically developed countries. It has been estimated to have an age-adjusted incidence rate of approximately 45 per 100,000 [1]. Approximately 150,000 new cases are diagnosed each year in the USA, with a similar number being diagnosed in Europe [2]. Mortality rates for colorectal cancer differ between the USA and Europe (17 per 100,000 vs. 21 per 100,000), resulting in differences in the overall 5-year survival rate (62 vs. 49%) [1].

One of the most important determinants of prognosis is the tumor stage at diagnosis. A recent evaluation of 119,363 colon cancer patients in the Surveillance, Epidemiology and End Results (SEER) National Cancer Registry from January 1st, 1991 to December 31st, 2000 showed that approximately a fifth of colon cancer patients had evidence of metastatic disease at the time of diagnosis (TABLE 1) [3]. These patients have a life expectancy of approximately 14–20 months [2], with an overall 5-year survival of 8.1% [3].

In the last 10 years there has been rapid development of agents with activity against colon cancer. These agents have been shown to be active not only in metastatic disease, but also in the adjuvant (nonmetastatic disease) setting. Current studies are investigating the roles of newer agents in the management of localized disease. These agents have been shown to be beneficial in the treatment of advanced disease. Attempts are being made to identify molecular characteristics of the tumor, which may help identify those patients who will derive a greater benefit from chemotherapy in the adjuvant setting. The treatment of advanced disease has shown improvements in response rates, which have translated into improvements in median survival times. The molecular characterization of tumors has led to the development of targeted therapies, which have shown a benefit when incorporated with more standard chemotherapeutic regimens. This review describes the standard chemotherapeutic options currently available for the treatment of the various stages of colon cancer.

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Stage-specific chemotherapy options for colon cancer

The stage of a cancer at diagnosis is one of the most important prognostic factors. Since 1959, the American Joint Committee on Cancer (AJCC) has been working on a system of classification based on the Tumor Node Metastasis (TNM) classification. As of January 1st, 2003, the sixth edition of the AJCC Cancer Staging Manual is being used to stage all new cancer cases [4]. For colon cancer, this edition stratifies Stages II and III further by the use of the T and N stages, resulting in a total of seven stages (TABLE 1). However, as yet, this subdivision of tumor stage does not affect treatment decisions.

Stage I colon cancer

Adjuvant chemotherapy is not a treatment option in Stage I colon cancer. The treatment is surgery with resection and anastomosis as the primary surgical option.

Stage II colon cancer

There is no definitive answer as to whether adjuvant chemotherapy should be added to the treatment of Stage II colon cancer. It has been estimated that the number of Stage II patients required to observe a statistically significant difference between treatment and observation arms would be 8000 at 3 years, 5800 at 4 years and 4700 at 5 years [5]. As a result, the studies of adjuvant chemotherapy in Stage II colon cancer should be interpreted cautiously as none of them have been adequately powered.

A SEER–Medicare cohort analysis for Stage II colon cancer practice patterns showed that a substantial minority of Stage II patients and/or their doctors perceive that the potential for a small increment in survival justified the treatment risks and discomforts [6]. It concluded that the continuation of a no-treatment control arm in Stage II randomized trials remained justified. However, in view of the relatively common usage of adjuvant chemotherapy in the setting of Stage II disease, the accrual to such trials may be difficult.

The International Multicenter Pooled analysis of B2 Colon Cancer Trials (IMPACT B2) was a meta-analysis of five different trials [7]. These trials involved Stage II patients who were randomized to either observation or treatment with 5-fluorouracil (5-FU) and leucovorin (LV). This study concluded that routine use of adjuvant chemotherapy was not indicated in Stage II colon cancer. A second meta-analysis was performed on the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials C-01 to C-06 [8]. This analysis concluded that adjuvant chemotherapy should be considered in Stage II patients as they appeared to receive a proportionate benefit similar to that seen for Stage III patients. A further meta-analysis of those trials in the IMPACT B2 meta-analysis in addition to two further trials was performed [9]. This analysis concluded that although patients with Stage II disease did receive a benefit from chemotherapy, the benefit was not as great as that seen with chemotherapy in Stage III colon cancer [9]. The data from this analysis were used to generate a model which can be used to derive prognostic and predictive information for an individual patient [101]. This model permits the patient and/or their doctor to derive applicable estimates regarding the risks and benefits of adjuvant chemotherapy.

Recent trials include the Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) [10] and the Quick and Simple and Reliable (QUASAR) collaborative group [11]. In the MOSAIC trial, approximately 40% of the patients were node negative. Although the survival curves of those Stage II patients in the treatment and control arms appeared to separate, they did not reach statistical significance. However, it should be noted that the control arm consisted of 5-FU/LV treatment rather than observation. The QUASAR trial recruited patients based on uncertainty (i.e., there were no definite indications for, or definite contraindications against, 5-FU, LV or levamisole [LEV] regimens). Patients with both colon and rectal tumors were entered, with 92% of the patients with Stage II disease. These patients were randomized to adjuvant treatment with 5-FU/LV-based chemotherapy or observation only with chemotherapy considered on recurrence. Small but statistically significant differences in favor of the treatment arm were observed for odds of recurrence and odds of death from colorectal cancer. This trial concluded that the small but definite survival benefits associated with chemotherapy outweighed the inconvenience and cost for high-risk and younger patients (<70 years of age).

Prior to the presentation of results from the QUASAR trial, the American Society of Clinical Oncology (ASCO) issued recommendations on the adjuvant treatment of Stage II colon cancer [12]. These recommendations concluded that although direct evidence does not support the routine use of chemotherapy for Stage II patients, the final decision on adjuvant chemotherapy should be taken after a full discussion of the evidence supporting treatment, anticipated side effects associated with treatment, presence of high-risk features and patient preferences.

Stage III colon cancer

In 1990, a National Institutes of Health (NIH) consensus conference recommended that adjuvant chemotherapy with 5-FU/LEV be the standard care for Stage III colon carcinoma [13]. These recommendations were based primarily on the results of two studies, the North Central Cancer Treatment Group (NCCTG) pilot study and Intergroup 0035. Over the next 10 years, a number of 5-FU/LEV and 5-FU/LV regimens were studied. Intergroup 0089 is considered by many as the definitive study of 5-FU regimens. This trial did not actually identify a best regimen based on efficacy [14]. However, given the duration of therapy required for the 5-FU/LEV arm, this regimen fell out of favor. As the addition of LEV to the Mayo Clinic regimen did not result in an increased benefit (TABLE 2), the use of LEV decreased. The two 5-FU/LV-containing regimens, the Roswell Park regimen (TABLE 2) and Mayo Clinic regimen, subsequently became the most commonly used regimens in the USA for Stage III colon cancer.

Table 1. Colon cancer stage (American Joint Committee on Cancer, Sixth Edition) at diagnosis and colon cancer-specific 5-year survivals (adapted from [3]).

Stage	Primary tumor, regional lymph node and distant metastasis requirements	Percentage at diagnosis	5-year survival (%)
I	Tumor invades either the submucosa (T1) or muscularis propria (T2) No regional lymph node metastasis (N0) No distant metastasis (M0)	15	93.2
IIa	Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues (T3) No regional lymph node metastasis (N0) No distant metastasis (M0)	30	84.7
IIb	Tumor directly invades other organs or structures including other segments of the colorectum by way of the serosa and/or perforates visceral peritoneum (T4) No regional lymph node metastasis (N0) No distant metastasis (M0)	6	72.2
IIIa	Tumor invades either the submucosa (T1) or muscularis propria (T2) Metastasis in 1–3 regional lymph nodes (N1) No distant metastasis (M0)	2	83.4
IIIb	Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues (T3), or tumor directly invades other organs or structures including other segments of the colorectum by way of the serosa and/or perforates visceral peritoneum (T4) Metastasis in 1–3 regional lymph nodes (N1) No distant metastasis (M0)	16	64.1
IIIc	Any primary tumor staging (T0–4) Metastasis in ≥4 regional lymph nodes (N2) No distant metastasis (M0)	9	44.3
IV	Any primary tumor staging (T0–4) Any regional lymph node staging (N0–2) Distant metastasis (M1)	22	8.1

M: Distant metastasis; N: Regional lymph node; T: Primary tumor.

Over the years, infusional 5-FU-containing regimens have also been investigated. Results from the setting of metastatic disease have shown that infusional therapy is at least as efficacious and less toxic than the bolus regimens. As a result, the infusional regimen LV5-FU2 has become popular. One trial compared the bolus regimen FUFOL with LV5-FU2 for 6 or 9 months [15]. In comparing the two arms, there was no significant difference in disease-free survival. However, overall there were significant differences with respect to the frequency of toxicities occurring in the two arms, with the infusional arm having a reduced incidence of neutropenia, diarrhea and mucosititis.

From this study came the MOSAIC trial. This study showed a substantive improvement in outcome beyond 5-FU/LV [10]. This was a prospective trial with patients randomized to receive either oxaliplatin and infusional 5-FU/LV (FOLFOX4) (TABLE 2) or LV5-FU2. These included both Stage II (40%) and III (60%) patients. The 3-year disease-free survivals for all patients were 77.8 and 72.9% for the FOLFOX4 and LV5-FU2 arms, respectively. This resulted in a hazard ratio of 0.77 (95% confidence interval [CI]: 0.65–0.92) or a 23% risk reduction in the FOLFOX4 arm. When Stage III patients were considered, 3-year disease-free survivals of 71.8 and 65.5% for the FOLFOX4 and LV5-FU2 arms, respectively, were observed, resulting in a hazard ratio of 0.76 (95% CI: 0.62–0.92) or a 24% risk reduction in the FOLFOX4 arm. The MOSAIC trial showed that while neutropenia was very common with the FOLFOX4 regimen (41 vs. 5%), febrile neutropenia was uncommon (0.7 vs. 0.1%). However, the main toxicity concern was the neurotoxicity associated with oxaliplatin in patients who might otherwise be cured. The incidence of neuropathy in the FOLFOX4 arm was 48, 32 and 12% for grades 1, 2 and 3, respectively. Although there was an improvement with time, and only 1% had grade 3 neuropathy 1 year after the discontinuation of therapy, more than 20% of all patients who received oxaliplatin still had some neuropathy at 18 months [10]. As a result of the MOSAIC trial, the FOLFOX4 regimen was established as the standard adjuvant chemotherapeutic regimen for the treatment of Stage III colon cancer patients. However, the toxicities and long-term effects need to be considered on an individual basis when decisions regarding treatment options are made.

Irinotecan, another agent which has been shown to be active in the metastatic setting, is currently being investigated in the adjuvant setting. An interim analysis of one trial, the Cancer

Table 2. Commonly used chemotherapeutic regimens.

Regimen	5-fluorouracil	Leucovorin	Oxaliplatin	Irinotecan
Mayo Clinic	425 mg/m^2 days 1–5 q 28 days x 6 cycles	20 mg/m^2 days 1–5 q 28 days x 6 cycles		
Roswell Park	500 mg/m^2 weekly x 6 q 8 weeks x 4 cycles	500 mg/m^2 weekly x 6 q 8 weeks x 4 cycles		
LV5-FU2	400 mg/m^2 bolus followed by 600 mg/m^2 infusion days 1 + 2 q 2 weeks x 12 cycles	200 mg/m^2 days 1 + 2 q 2 weeks x 12 cycles		
FOLFOX4	400 mg/m^2 bolus followed by 600 mg/m^2 infusion days 1 + 2 q 2 weeks x 12 cycles	200 mg/m^2 days 1 + 2 q 2 weeks x 12 cycles	85 mg/m^2 day 1 q 2 weeks x 12 cycles	
FOLFOX6	400 mg/m^2 bolus day 1 followed by 2,400–3000 mg/m^2 infusion over 46 h q 2 weeks x 12 cycles	200 mg/m^2 day 1 q 2 weeks x 12 cycles	100 mg/m^2 day 1 q 2 weeks x 12 cycles	
IFL	500 mg/m^2 weekly x 4 q 6 weeks x 5 cycles	20 mg/m^2 weekly x 4 q 6 weeks x 5 cycles		125 mg/m^2 weekly x 4 q 6 weeks x 5 cycles
FOLFIRI	400 mg/m^2 bolus day 1 followed by 2,400–3000 mg/m^2 infusion over 46 h q 2 weeks x 12 cycles	200 mg/m^2 day 1 q 2 weeks x 12 cycles		180 mg/m^2 day 1 q 2 weeks x 12 cycles

FOLFOX: 5-fluorouracil, leucovorin and oxaliplatin; FOLFIRI: 5-fluorouracil, leucovorin and irinotecan; FU: fluorouracil; IFL: Irinotecan, 5-fluorouracil (administered as a bolus) and leucovorin; LV: Leucovorin; q: Every.

and Leukemia Group B (CALGB) Intergroup Trial C89803, was recently presented [16]. This is a Phase III trial of irinotecan and bolus 5-FU/LV (IFL) versus the Roswell Park regimen and was designed to investigate whether the improvements reported with irinotecan administration to Stage IV patients translated to the adjuvant setting [17–19]. Overall, there appeared to be no differences between the IFL and control arms in terms of clinical benefit. The IFL regimen was associated with greater toxicity and greater risk of early death. Although the results presented were from a planned interim analysis, it was reported that these would be the final results, as futility boundaries had been crossed and it could not be a positive study with additional follow-up [16].

The failure of IFL to show a clinical benefit in adjuvant treatment may be due to a lack of irinotecan activity in the adjuvant setting, or it may be as a result of the 5-FU component of the regimen. This latter possibility should be answered by the results of the Pan European Trials in Adjuvant Colorectal Cancer (PETACC) III and the Fondation Française de Cancérologie Digestive Adjuvant ACCORD II trials. Both trials have randomized patients to treatment with 5-FU, LV and irinotecan (FOLFIRI) versus LV5-FU2 and are expected to report their results in early 2005.

Oral fluoropyrimidines (capecitabine and uracil-tegafur [UFT]) have also been investigated in the setting of adjuvant chemotherapy. The Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) study, a Phase III trial, randomized patients with Stage III colon cancer to treatment with either capecitabine (1250 mg/m^2 twice daily days 1–14, every 21 days) or the Mayo Clinic regimen [20]. The primary end point was disease-free survival, with the study powered to detect equivalence rather than superiority. Equivalence was demonstrated between the two arms with a trend towards improved disease-free survival and overall survival in favor of the capecitabine arm. The dose of capecitabine in this trial was higher than that usually administered. However, due to close monitoring of patients and careful attention to dose reductions and treatment delays, nearly half of the patients received the full dose. With the exception of hand–foot syndrome, all other parameters (diarrhea, stomatitis, neutropenia, nausea, vomiting and alopecia) favored capecitabine [21]. The other oral agent, UFT, has also been compared with 5-FU/LV in the adjuvant setting [22]. This trial randomized patients with Stage II or III colon cancer to receive both UFT and LV orally or the Roswell Park regimen for three cycles. Similar disease-free rates, overall survivals and toxicities were observed in both arms, with significant differences in terms of quality of life parameters in favor of the UFT/LV arm. At the present time, UFT is not available in the USA.

Stage IV colon cancer

5-FU was patented in the 1950s, and 10 years ago was the focus of virtually all the regimens used in the treatment of advanced disease. There are now five additional agents which have been shown to have activity in the setting of advanced disease.

Irinotecan

Irinotecan's role in the treatment of advanced colon cancer was solidified by the results of studies analyzing irinotecan versus best supportive care in patients who had previously failed 5-FU frontline therapy [23]. This study found significant differences in 6-month and 1-year survival in favor of the irinotecan arm ($p = 0.0001$). The results of this study suggested that 1-year survival was twice as high for those receiving irinotecan as those who received best supportive care, and that informal quality of

life assessment was as good or better in the irinotecan arm. This study supported the idea that patients with advanced disease could receive more than one round of chemotherapy, raising the possibility of adding irinotecan to 5-FU. The downside of this, however, was that there were overlapping toxicities, primarily diarrhea and neutropenia.

There are three advanced disease trials examining the benefit derived from addition of irinotecan to 5-FU/LV [16–18]. Consistently, results were observed in favor of the addition of irinotecan to 5-FU/LV, with an approximate doubling of response rates and associated improvements in time to progression and overall survival.

Oxaliplatin

At the same time there was a Phase III trial investigating the contribution of oxaliplatin when added to a 5-FU/LV-based regimen (FOLFOX4) [24]. Although this study showed improvements in response rate and progression-free survival, the increase in median survival did not reach statistical significance ($p = 0.12$). There were increases in the rate of grade 3/4 neutropenia and diarrhea, together with oxaliplatin-associated neurotoxicity.

In an attempt to sort regimens in terms of efficacy, the NCCTG/Intergroup study N9741 originally assigned patients to one of six treatment arms. However, following the publication of results from advanced disease trials, some of the treatment arms were dropped, leaving three arms. These were IFL, FOLFOX4 and irinotecan and oxaliplatin (IROX). The important information from this trial was that the efficacy data showed that FOLFOX4 appeared to be superior to IFL in terms of median survival (19.5 vs. 15.0 months; $p = 0.0001$), time to progression (8.7 vs. 6.9 months; $p = 0.0014$) and response rate (45 vs. 31%; $p = 0.002$) [25].

Although the N9741 study showed efficacy results favoring FOLFOX4, this study did not clearly address the question of whether the differences observed between oxaliplatin and irinotecan treatment were due to the individual agents themselves or to the 5-FU/LV schedules with which they were coadministered. This issue has also been raised in the adjuvant setting as a possible explanation for the apparent lack of improvement with IFL administration to patients with Stage III colon cancer. This question was addressed by a study comparing the efficacies of the FOLFOX and FOLFIRI regimens in the first-line treatment of metastatic colorectal cancer [26]. This study randomized patients with metastatic colorectal cancer to treatment with either the FOLFOX or FOLFIRI regimens and mandated a crossover to the opposite treatment at the time of disease progression. No difference in overall survival was noted between the two arms. Either FOLFOX or FOLFIRI would appear to be a reasonable first-line approach in the treatment of advanced colorectal cancer. Data either corroborating or refuting these findings will be available upon completion of the CALGB trial 80203, in which patients with previously untreated metastatic colorectal cancer are randomized to treatment with either FOLFOX with or without cetuximab or FOLFIRI with or without cetuximab.

Capecitabine

Capecitabine has been compared with 5-FU/LV in the setting of advanced disease in two large Phase III trials [27]. The response rate, time to progression and overall survival were 26%, 4.6 months and 12.9 months, respectively, for the capecitabine arms. When compared with the 5-FU/LV arms (17%, 4.7 months and 12.8 months, respectively), response rate to capecitabine was significantly better ($p < 0.0002$). Trials investigating combinations of capecitabine are currently underway. One such study design is the European Organization for Research and Treatment of Cancer (EORTC) trial 40015. This is a Phase II trial that has randomized 692 patients with previously untreated metastatic colorectal cancer to treatment with irinotecan and 5-FU/LV with or without celecoxib or irinotecan and capecitabine with or without celecoxib. There is much interest regarding whether or not capecitabine can replace infusional 5-FU therapy. The efficacy of the capecitabine–oxaliplatin with or without bevacizumab combination versus FOLFOX4 with or without bevacizumab in the first-line treatment of metastatic colorectal cancer is being studied. The oral agent UFT was also investigated in the setting of advanced disease. Two Phase III studies compared the efficacy of UFT/LV with the Mayo Clinic regimen of bolus 5-FU administration [28,29]. Both studies showed no significant differences in response rate, time to progression and overall survival between the two arms. There were significant reductions in toxicities such as diarrhea, nausea and vomiting, mucosititis and myelosuppression on the UFT arm.

Cetuximab

Cetuximab, the immunoglobulin G1 antibody to the epidermal growth factor receptor (EGFR), was approved as a treatment option in irinotecan failures in February 2004. The original Phase II trial was performed in combination with irinotecan [30]. This trial randomized patients who previously failed irinotecan therapy to treatment with either irinotecan and cetuximab ($n = 121$) or cetuximab alone ($n = 57$). There were 22.5% partial responses on the irinotecan and cetuximab arm compared with 10.5% on the cetuximab-only arm. Median response duration was reported to be 6.2 and 4.2 months, respectively. A confirmatory Phase II trial in Europe (the BOND trial) again randomized patients failing irinotecan therapy to cetuximab monotherapy or irinotecan and cetuximab. Similar partial response rates were observed (22.9 vs. 10.8%) with median times to progression of 4.1 versus 1.5 months [31]. As a result of these trials, cetuximab was approved in the USA and several other countries for use in the setting of advanced disease which had progressed on an irinotecan-containing regimen.

Bevacizumab

The antiangiogenic antibody bevacizumab is a humanized antivascular endothelial growth factor (VEGF) monoclonal antibody that binds and neutralizes all forms of VEGF-A and has a half-life of 17–21 days. The first important trial of this antibody in colorectal cancer was a Phase II trial in which

patients with previously untreated metastatic colorectal cancer were randomized to treatment with 5-FU/LV until progression, and then treated with bevacizumab (10 mg/kg) or 5-FU/LV with concurrent administration of bevacizumab (5 or 10 mg/kg) [32]. This trial showed slightly better results for the arm containing the lower dose of bevacizumab (5 mg/kg) administered concurrently with 5-FU/LV. This dose was selected for use in a Phase III trial investigating bevacizumab as first-line therapy in advanced disease [33]. Patients were randomized to treatment with IFL and placebo or IFL and bevacizumab. The bevacizumab treatment arm had statistically significant increases in median survival (20.3 vs. 15.6 months; hazard ratio: 0.65; $p = 0.00004$), progression-free survival (10.6 vs. 6.24 months; hazard ratio: 0.54; $p < 0.00001$), overall response rate (45 vs. 35%; $p = 0.0036$) and duration of response (10.4 vs. 7.1 months; $p = 0.0014$). Analysis of the adverse events occurring in this trial showed that there was not a significant increase in deep venous thrombosis (DVT) or bleeding in the bevacizumab-treated patients. There were increases in the number of patients developing hypertension and a slight increase in the number developing diarrhea and neutropenia. One unexpected adverse event was gastrointestinal perforation with six cases being observed in this study, one resulting in death.

General guidelines for treating metastatic colon cancer indicate that first-line monotherapy should be considered in those patients with compromised performance status or with comorbid illnesses such as liver and/or renal dysfunction. Monotherapy accounts for approximately 30% of treatments in the USA and results in a response rate of 15–30% and a median survival of 11–14 months. Treatment options consist primarily of 5-FU/LV regimens or treatment with capecitabine. In the USA, combination therapy accounts for approximately 70% of treatments and results in a 35–50% response rate with a median survival of 15–21 months. When sequential therapy incorporating different combination regimens with or without single agents are used, the median survival can be extended to 20–26 months. First-line combination therapy options are primarily 5-FU-based, combined with either irinotecan or oxaliplatin. The irinotecan–5-FU combinations are administered either as a bolus (e.g., IFL [18]) or as an infusion (e.g., FOLFIRI [17]).When the performance metrics of these regimens are compared, the infusional regimens appear to be associated with higher clinical efficacies and reduced toxicities than the bolus regimen. The oxaliplatin-containing regimens can likewise be administered as infusion or bolus schedules. The infusional regimens are primarily variations of FOLFOX4 [24], being FOLFOX6 [26] or FOLFOX7 [34], whereas the principal bolus regimen is bFOL [35]. Again, when the performance metrics reported for these various regimens are compared with each other, the trend in response rate, median survival and adverse events appears to favor the infusional regimens. However, all the schedules developed in Phase III studies have been with infusional 5-FU regimens. Although all the regimens have not been compared face to face, from the data published to date, no one regimen appears to be superior to another in the setting of advanced disease. However, it has been shown that the median survival of patients correlates positively with the availability of all known active chemotherapeutic agents to all patients [36].

Summary & conclusions

Patients diagnosed with colon cancer should be offered the option of participating in a clinical trial.

At the present time, routine use of adjuvant chemotherapy for Stage II colon cancer is not supported by direct evidence from randomized controlled trials. A decision in favor of chemotherapy can only be made following a full discussion of:

- The current evidence
- The estimated benefit of chemotherapy derived from tools such as the Gill model
- The side effects both in terms of quality of life during chemotherapy, and longer term sequelae such as neuropathy if an oxaliplatin-containing regimen is considered

For Stage III colon cancer patients, although the current evidence for adjuvant chemotherapy uses the FOLFOX4 regimen, in the USA, a modified version of FOLFOX6 (mFOLFOX6, with a reduced oxaliplatin dose of 85 mg/m^2), is becoming increasingly popular as the adjuvant regimen of choice. Where medical conditions, such as multiple sclerosis or diabetic neuropathy, or the patient's occupation make the use of oxaliplatin undesirable, the 5-FU/LV regimens remain valid alternative options in the adjuvant setting. The oral agents capecitabine and UFT may be considered as alternative agents in suitable patients, particularly those with compromised performance status. Irinotecan as administered in the IFL regimen is not a valid option in the adjuvant setting. Whether irinotecan confers a benefit in the adjuvant setting should become clearer with the results of the Pan-European Trials In Adjuvant Colon Cancer (PETACC) III and ACCORD II trials, where irinotecan was administered with the infusional LV5-FU2 regimen rather than a bolus 5-FU/LV regimen.

Currently, there are a number of regimens which have clinical efficacy in advanced colon cancer. The two principal regimen types are those adding oxaliplatin or irinotecan to 5-FU backbones. The choice of which regimen for use as first-line treatment does not appear to significantly impact the overall survival [26]. This complexity has been increased further with the demonstration of clinical efficacy of monoclonal antibody therapy. These agents appear to be more efficacious when used in combination with other chemotherapeutic agents rather than as monotherapy. However, the most efficacious combination of these agents is still to be determined.

Expert commentary

Although the current ASCO recommendations do not support the routine use of adjuvant chemotherapy in Stage II colon

cancer, there is a perception among patients and their physicians that the potential for a small increase in survival justifies the costs and side effects of adjuvant treatment. Currently, chemotherapy is considered a valid option in high-risk Stage II patients, which include those presenting with obstruction and/or perforation. This view is certainly supported by the fact that the colon cancer-specific 5-year survival for Stage IIB colon cancer appears to be worse than that for Stage IIIA (72 vs. 83%; $p < 0.001$) [3]. Another factor which may influence decisions regarding chemotherapy is the number of resected lymph nodes. This has been shown to have prognostic implications by itself [37], and it has been suggested that a minimum of 12–15 nodes need to be collected in order to reliably decide that a patient is, in fact, node negative [38]. Further attempts to stratify patients into high- and low-risk groups are ongoing. These are based on the molecular characteristics of the tumor itself, such as loss of heterozygozity (LOH) of chromosome 18q [39], lack of microsatellite instability (MSI) [40,41], and microarray identification of high-risk gene cluster pattern of expression [42].

The standard adjuvant regimen of Stage III cancer is FOLFOX4. As the analysis of toxicities in the MOSAIC trial showed, a quarter of all patients treated had some form of neuropathy up to 18 months after the discontinuation of treatment. The possibility of long-term treatment-induced morbidity in the adjuvant setting remains a serious consideration for both the patient and their physician. The results of the CALGB Intergroup Trial C89803 demonstrates, once again, the importance of well-structured trials in oncology [19]. Prior to this trial, it had widely been assumed that IFL would be active in the adjuvant setting given its activity in metastatic colon cancer [17]. As this trial showed, however, the irinotecan-containing regimen, IFL, has no role to play in the adjuvant treatment of colon cancer. Whether this lack of benefit is a reflection of a lack of action of irinotecan in the adjuvant setting, or is a result of the 5-FU/LV regimen with which it is administered, should be answered when the results of the PETACC III and ACCORD II trials become available.

At the present time, no one regimen has been shown to be superior to another in the setting of advanced disease. Although capecitabine combinations have interesting and compelling Phase II data, this is not necessarily an adequate reason to use these combinations routinely in practice. However, there may be certain circumstances in which this approach seems appropriate.

Five-year view

With respect to Stage II patients, recruitment into trials such as ECOG 5202 should help identify if particular subsets of Stage II patients derive more benefit from chemotherapy than others. In this trial, Stage II patients are stratified into high- and low-risk groups depending on the molecular characteristics of their tumors (18q LOH and/or absence of MSI being considered indicators of high risk). High-risk patients are randomized to receive FOLFOX or FOLFOX and bevacizumab while low-risk patients are observed.

The question of irinotecan activity in the adjuvant setting should be answered with the results from the PETACC III and ACCORD II trials. The activity of the targeted therapies, bevacizumab and cetuximab, in the adjuvant setting should also become clearer.

In the setting of advanced disease, patients have been selected for cetuximab treatment by the presence of EGFR on the cell surface. However, this may not be the best way of choosing these patients as even in those patients who had more than 10% detectable EGFR, there was a 23% response rate in the combination arm, which was almost the same as that achieved in those patients with more than 35% EGFR expression [31]. An industry-sponsored Phase II trial (CP02–0451) is currently underway to determine if cetuximab has any effect on EGFR-negative tumors. Cetuximab- and irinotecan-based chemotherapy has also been investigated as frontline treatment for metastatic colorectal carcinoma in a number of small trials, which reported overall response rates of 48–74% [43–45]. Although the response rates of these early clinical trials are very encouraging, the results need to be confirmed in larger series.

There are currently several trials whose results should answer important questions regarding bevacizumab. One such trial is ECOG R3200, a Phase III trial of bevacizumab in combination with FOLFOX4 as second-line treatment. Data regarding the efficacy of bevacizumab as second-line therapy in advanced disease should become available with the maturation of this trial.

CALGB 80302 (a Phase III trial designed to investigate cetuximab as first-line treatment in patients with advanced disease) and SWOG 0303 (a Phase III trial designed to investigate the use of bevacizumab in the first-line treatment of advanced disease in association with oxaliplatin administered as FOLFOX or in association with capecitabine) have been closed because both contained arms with no antibody and were accruing very slowly. The SWOG and CALGB are leading a jointly sponsored trial which has been approved by CTEP but not yet activated. This trial plans to recruit approximately 2500 patients, with randomization to treatment arms with either FOLFOX or FOLFIRI plus either cetuximab, bevacizumab or both antibodies.

Recently, the Oncologic Drugs Advisory Committee of the FDA accepted 3-year disease-free survival as a surrogate end point for 5-year overall survival in the adjuvant setting. This decision was made following the statistical analysis of numerous prior studies which concluded that there was a very close correlation between these two parameters [46]. The acceptance of this parameter as a surrogate end point should facilitate the interpretation of future studies.

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Key issues

- Where possible, patients should be offered participation in trials.
- In patients with Stage II disease, a thorough discussion of the risks and benefits of adjuvant chemotherapy should take place prior to deciding on treatment directions.
- Current data supports the use of the oxaliplatin and infusional 5-fluorouracil/leucovorin (FOLFOX4) regimen as the standard of care in Stage III patients.
- Trial results to date do not provide compelling evidence in support of any one regimen over another as the standard of care of metastatic colon cancer.
- In the setting of advanced disease, oxaliplatin- and irinotecan-containing regimens appear comparable, with differing toxicity profiles. Infusional schedules of 5-fluorouracil are now considered standard in view of the reduced toxicity of these schedules when compared with bolus 5-fluorouracil administration. However, the best combination of agents to be used in the first-line treatment of colon cancer remains to be defined.
- In order to maximize results, all active agents must be available to all patients.
- Given the cost of newer agents, future developments must include the identification of factors which will aid in the individualization of therapy.
- Although the treatment of colon cancer is improving, it is also getting more complicated. However, colorectal cancer remains the second most common cause of cancer death in the USA and despite substantial advances, chemotherapeutic options for this disease remain inadequate.
- Numerous clinical trials of new drug combinations and new strategies are currently underway. These trials must continue to receive high priority.

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Affiliation

- *Michael J Martin, MB, PhD, MRCPI, MRCP(UK) Medical Oncology Clinical Research Unit and Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 6120 Executive Blvd, EPS, Rm 7016, Rockville, MD 20852, USA*
Tel.: +1 301 451 9732
Fax: +1 301 496 1854
martmich@mail.nih.gov